

Solid Tumour Section

Mini Review

Soft tissue tumors: Liposarcoma / malignant lipomatous tumors

Nils Mandahl

Department of Clinical Genetics, Lund University Hospital, 221 85 Lund, Sweden (NM)

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Identity

Note

Liposarcomas are adipose tissue tumors, including low-malignant to highly malignant subtypes, constituting 10-15% of soft tissue sarcomas.

Classification

Well-differentiated liposarcoma: the well-differentiated liposarcomas are tumors of low grade malignancy that may recur locally but not metastasize; the terminology of subtypes is not straightforward; three related subtypes have been distinguished: lipoma-like (the most common form), inflammatory, and sclerosing; other terms that have been suggested to describe at least subsets of these tumors are atypical lipoma and atypical lipomatous tumor.

Myxoid liposarcoma/round cell liposarcoma: myxoid liposarcoma is the most common form of liposarcomas, constituting about half of the cases, with a relatively favorable prognosis; the much less common, and more aggressive round cell liposarcoma is regarded as a poorly differentiated variant of myxoid liposarcoma; pure round cell liposarcomas are very rare, and more often the tumors represent mixed liposarcomas with both myxoid and round cell components at different proportions; in recurrences the round cell component may increase.

Pleomorphic liposarcoma: the pleomorphic liposarcomas are highly malignant tumors showing a disorderly growth pattern and extensive cellular pleomorphism.

Clinics and pathology

Epidemiology

The reported annual incidence of liposarcoma is in the range of 2.5 per million; liposarcomas are tumors of adult life with a median age of 55-60 years; patients younger than 15 years are rare; men are slightly more often affected than women.

Clinics

The major sites are the lower extremities and the retroperitoneum; most tumors range from 5 to 10 cm in diameter, but much larger tumors are not rarely seen.

Evolution

The risk of distant metastases relate to the type and degree of histological differentiation; well-differentiated liposarcomas may occasionally dedifferentiate to highly malignant tumors that may metastasize.

Prognosis

The survival rates are primarily dependent on the histological type, and patients with well-differentiated and myxoid liposarcomas, on the one hand, fare much better than round cell and pleomorphic liposarcomas on the other hand.

Cytogenetics

Cytogenetics Morphological

Well-differentiated liposarcoma / atypical lipomatous tumor

The vast majority of this subset of tumors, irrespective of whether classified as atypical lipomatous tumor, atypical lipoma, or well-differentiated liposarcoma, is characterized by the presence of one or more supernumerary ring chromosome or giant marker chromosome.

Frequently, these show an extensive intratumor variability in size and number; this has been attributed to mitotic irregularities due to breakage-fusion-bridge cycles, which are also associated with the observed nuclear atypia.

In about one-third of the cases, there are, in addition to rings and markers, a few other numerical and/or structural aberrations; these changes do not show any obvious non-random pattern, with the exception of loss of 13q material.

Another characteristic feature, seen in the majority of these tumors, is the high frequency of telomeric associations, showing a non-random pattern with a preferential involvement of the 11p telomere.

Some tumors with minimal atypia have been reported to show gain of 12q15-q24 sequences rather than rings and markers or balanced translocations of 12q13-15, which is a typical feature of benign, ordinary lipomas.

Cytogenetics Molecular

The ring and giant marker chromosomes have been shown to contain regularly material from 12q and, occasionally, material from another chromosome that may vary from case to case, except for the frequent occurrence of amplified sequences from 1q21 in inter-/intramuscular tumors.

Several tumor-associated genes, localized to 12q13-q21, are amplified; these include in particular MDM2, but also SAS, CDK4, and HMGIC; the size of the amplicon vary, and two or more of these genes as well as other sequences may be co-amplified, although frequently at different levels; with few exceptions, MDM2 is not only amplified but also overexpressed.

Most rings are negative for chromosome specific centromere probes by FISH, but have centromeric activity as indicated by the positivity for anti CENP-C antibodies.

Cytogenetics Morphological

Myxoid liposarcoma / round cell liposarcoma:

The specific rearrangement t(12;16)(q13;p11), or variants involving one or more additional chromosomes in complex translocations, is found in about 90% of myxoid liposarcomas, including tumors with a mixture of myxoid and round cell components; in one-third of the cases this translocation is the sole cytogenetic anomaly; the most common secondary aberration, seen in 6-7% of the cases, is trisomy 8.

The alternative t(12;22)(q13;q12), most often seen in seemingly unbalanced or in complex rearrangements, has been identified in about 5% of the cases; it should be noted that a cytogenetically, but not molecularly, indistinguishable 12;22-translocation has been

identified as the characteristic aberration in clear cell sarcoma of the tendons and aponeuroses.

Among the few cases reported as pure round cell liposarcoma that have been investigated cytogenetically, t(12;16) is rare and the majority of cases have had fairly complex, unspecific aberrations.

Cytogenetics Molecular

The molecular genetic consequences of the t(12;16) is the formation of a fusion gene, involving FUS in 16p11 and CHOP in 12q13, encoding a chimeric protein; different fusion transcripts have been identified, containing the 5' promoter part of FUS, most often with exons 1-5 or alternatively either exons 1-7 or 1-8, and the entire coding region of CHOP, i.e., exons 1-4 or 2-4; this gene fusion may be identified by RT-PCR as well as by genomic PCR; the CHOP protein belongs to the C/EBP family of basic leucine zipper group of transcription factors.

The rearrangements involving 12q13 and 22q12 result in a related gene fusion, affecting the EWS and CHOP genes; thus, the two closely related genes FUS and EWS seem to be interchangeable when fused to CHOP; both FUS and EWS carry a central RNA-binding RNP-1 motif, and possibly these proteins can also bind to DNA.

Cytogenetics Morphological

Pleomorphic liposarcoma

Few cases have been cytogenetically characterized; they invariably show complex karyotypic changes, with no characteristic changes identified, and an extensive intratumor heterogeneity.

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